Decrease of gray matter volume in the midbrain is associated with treatment response in medication-overuse headache: Possible influence of orbitofrontal cortex

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Abstract: Patients with chronic daily headache and overuse of analgesics, triptans, or other acute headache compounds, are considered to suffer from medication-overuse headache (MOH). This implies that medication overuse is the cause of headache chronification. It remains a key question why only two-thirds of patients with chronic migraine-like headache and overuse of pain medication improve after detoxification, whereas the remainder continue to have chronic headache. In the present longitudinal MRI study, we used voxel-based morphometry to investigate gray matter changes related to medication withdrawal in a group of humans with MOH. As a main result, we found that only patients with significant clinical improvement showed a significant decrease of previously increased gray matter in the midbrain including periaqueductal gray matter and nucleus cuneiformis, whereas patients without improvement did not. Patients without treatment response had less gray matter in the orbitofrontal cortex. Another striking result is the correlation of treatment response with the amount of orbitofrontal gray matter. Thus, we demonstrate adaptive gray matter changes within the pain modulatory system in patients with MOH who responded to detoxification, probably reflecting neuronal plasticity. Decreased gray matter in the orbitofrontal cortex at baseline may be predictive of poor response to treatment.

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Development/Plasticity/Repair

Decrease of Gray Matter Volume in the Midbrain is Associated with Treatment Response in Medication-Overuse Headache: Possible Influence of Orbitofrontal Cortex

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Patients with chronic daily headache and overuse of analgesics, triptans, or other acute headache compounds, are considered to suffer from medication-overuse headache (MOH). This implies that medication overuse is the cause of headache chronification. It remains a key question why only two-thirds of patients with chronic migraine-like headache and overuse of pain medication improve after detoxification, whereas the remainder continue to have chronic headache. In the present longitudinal MRI study, we used voxel-based morphometry to investigate gray matter changes related to medication withdrawal in a group of humans with MOH. As a main result, we found that only patients with significant clinical improvement showed a significant decrease of previously increased gray matter in the midbrain including periaqueductal gray matter and nucleus cuneiformis, whereas patients without improvement did not. Patients without treatment response had less gray matter in the orbitofrontal cortex. Another striking result is the correlation of treatment response with the amount of orbitofrontal gray matter. Thus, we demonstrate adaptive gray matter changes within the pain modulatory system in patients with MOH who responded to detoxification, probably reflecting neuronal plasticity. Decreased gray matter in the orbitofrontal cortex at baseline may be predictive of poor response to treatment.

Introduction

Medication-overuse headache (MOH) is a complication of migraine that causes significant social and financial burden. MOH is defined as headache for ≥15 days per month that develops, or significantly worsens, during medication overuse (Headache Classification Subcommittee of the International Headache Society, 2004; Olesen et al., 2006). According to the diagnostic criteria of the Headache Classification Subcommittee of the International Headache Society (2004), MOH could only be diagnosed if chronic headache returned to its episodic pattern after the cessation of medication overuse. Thus, the diagnosis of MOH could only be made retrospectively. In 2006, a broader definition of MOH was proposed (Olesen et al., 2006) in which the improvement after withdrawal was no longer mandatory, thus allowing for a prospective diagnosis.

Recent studies demonstrated metabolic and structural abnormalities in MOH (Fumal et al., 2006; Riederer et al., 2012). In a PET study, persistent hypometabolism was found in orbitofrontal cortex (OFC), whereas other dysmetabolic regions returned to normal after withdrawal (Fumal et al., 2006). Since hypofunction of the OFC is known to occur in drug dependence, it was suggested that this may predispose subgroups of persons who experience migraine headaches to recurrent medication overuse (Fumal et al., 2006). Voxel-based morphometry (VBM) is a powerful tool with which to study neurological disease, with the detection of structural changes in the brain being operator independent (Ashburner and Friston, 2000; Whitwell, 2009). In a VBM study, we found gray matter (GM) changes in structures related to pain processing and antinociception (Riederer et al., 2012). Specifically, GM increases were found in the periaqueductal gray of the midbrain (PAG), the thalamus, and the striatum, and decreases were found in frontal regions, including OFC and the insula.

The PAG is a substantial component of the descending pain modulatory network and exerts an inhibitory or excitatory control on nociceptive transmission via the rostral ventromedial medulla (RVM), which in turn projects to the spinal and medullary dorsal horn (Heinricher et al., 2009; Benarroch, 2012). While it is widely accepted that that the brainstem plays a pivotal role in migraine pathophysiology (Raskin et al., 1987; Weiller et al., 1995; Veloso et al., 1998; Welch et al., 2001; Afridi et al., 2005), dysfunction of descending pain modulatory systems with a shift toward pain facilitation has recently been suggested in MOH (Perrotta et al., 2010, 2012). Importantly, abnormal processing of pain stimuli and impaired su-

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praspinal pain control in patients with MOH improved after detoxification.

Here we investigated whether the GM changes associated with MOH in humans, such as increase in the midbrain, thalamus, and striatum, and decrease in frontal regions (Riederer et al., 2012), were reversible after detoxification. Assuming that VBM detects neuroplasticity in adults (Draganski et al., 2004; May, 2011), we hypothesized neuroplastic changes particularly in brainstem and frontal cortex in patients with significant clinical improvement (responders), but not in the patients without improvement (nonresponders).

Further, we investigated whether regional GM changes at baseline would distinguish between responders and nonresponders, and thus predict treatment response, focusing on OFC. To test these hypotheses, high-resolution structural MRIs were performed in MOH patients before and after detoxification.

Materials and Methods

This is an extension of a previously published study (Riederer et al., 2012). The study was approved by the ethics committee of the Canton Zurich. Written informed consent was obtained from all study participants according to the Declaration of Helsinki.

Subjects. Thirty-eight patients with MOH, according to the proposed revision of criteria of the Headache Classification Subcommittee of the International Headache Society (2004) by Olesen (Olesen et al., 2006), were included in the study. Medication overuse was defined as treatment with the following acute/symptomatic treatment drugs: ergotamine, triptans, opioids, or combination analgesic medications ≥10 d/month; or simple analgesics or any combination of ergotamine, triptans, or analgesics opioids without overuse of any single class alone ≥15 d/month (Headache Classification Subcommittee of the International Headache Society, 2004; Olesen et al., 2006) on a regular basis for ≥3 months.

Headache days per month and days with pain medication per month were recorded during a baseline period at least 1 month before scan 1 and in the month before scan 2, which was scheduled at least 3 months after scan 1, based on headache diaries. Patients were considered as responders if they had a reduction of ≥50% in headache days per month at follow-up. Each responder was age and gender matched to a corresponding nonresponder. Patients with known abnormalities in brain imaging (MRI or CT scans) were not included.

Structural MRI. High-resolution structural MRI was performed in all patients before medication withdrawal and 3 months after. All MRI data were obtained on a 3 tesla Philips Achieva scanner (Philips Medical Systems) at the Institute for Biomedical Engineering, Swiss Federal Institute of Technology and University of Zurich. The T1-weighted volume sequences of the whole brain were acquired using a three-dimensional magnetization-prepared rapid acquisition gradient echo sequence (TR, 8.7 ms; TE, 2.3 ms; flip angle, 8.0°; voxel size, 0.86 × 0.86 × 1.0 mm; axial slice orientation, matrix size 256 × 256).

Voxel-based morphometry. Images were analyzed with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), incorporated in the SPM8 software running on MATLAB R2008b (MathWorks). The longitudinal preprocessing approach integrated into the VBM8 toolbox was used (Bezzola et al., 2011). In brief, the following steps were performed: (1) registration of time point 2 scan to time point 1 scan for each subject separately; (2) intrasubject bias correction; (3) segmentation into different tissue classes; (4) linear and nonlinear registration; and (5) modulation of tissue segments by the nonlinear normalization parameters to account for individual brain size differences. The normalized GM segments were smoothed using a 6 mm FWHM Gaussian kernel.

Statistical analysis. Clinical data were analyzed with IBM SPSS Statistics 20 program. Student's *t* tests were used to compare parametric data and Mann–Whitney *U* tests for nonparametric data.

Imaging data were analyzed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). First, baseline and follow-up scans were compared in responders and nonresponders matched for age and sex, using a repeated-measures ANOVA (flexible-factorial) model with within-subject factor time (T1, T2) and between-subjects factor group (responders, nonresponders), testing for a group × time interaction. T-contrasts were defined to identify regions with significant GM decrease or increase from scan 1 to scan 2 in responders and nonresponders, respectively. The resulting set of voxels for each contrast was thresholded at $p < 0.05$, corrected for multiple comparisons with familywise error. For predefined regions (midbrain, thalamus, insula, striatum, OFC, and prefrontal cortex), a region of interest (ROI) analysis was performed, using WFU-PickAtlas (at $p < 0.05$, corrected).

Subsequently, baseline scans of responders and matched nonresponders were compared using a two-sample *t* test model. Total GM volume was used as nuisance variable. Here, SPM small-volume correction (sphere with a radius of 10 mm, at $p < 0.05$) within the predefined ROIs was used. For all analyses, an extent threshold of a minimum of 5 voxels was used. All coordinates are given in Montreal Neurological Institute (MNI) space. In the significant cluster in the OFC cortex that resulted from baseline comparisons, individual GM volumes of all patients were extracted using the marsbar toolbox and correlated with treatment response (defined as the percentage reduction in headache days at follow-up) within SPSS.

Possible correlation of cerebral GM at baseline with intake of acute medication (days with pain medication per month) were investigated in a multiple regression model within SPM8, including total GM volume, age, and gender as nuisance variables. Whole-brain and ROI analyses using WFU-PickAtlas (at $p < 0.05$, corrected) were performed.

Table 1. Demographic and clinical data in patients with MOH

	Responders ($N = 11$)	Nonresponders ($N = 11$)	*p* value[a]
Time between scans (d)	113.2 ± 42.6	107.3 ± 32.3	0.720 (*t* test)
Age (years)	41.8 ± 9.1	44.3 ± 12.0	0.365
Gender (female/male)	9/2	9/2	NA
Headache			
d/month at baseline	25.0 ± 6.8	26.2 ± 5.3	0.652
% reduction	73.4 ± 10.1	18.7 ± 27.5	<0.001
Receiving medication			
d/month at follow-up	6.4 ± 4.9	12.8 ± 9.4	0.047
Δd/month at follow-up	−14.2 ± 8.7	−10.4 ± 10.8	0.300
Headache duration (years)	20.1 ± 12.2	19.0 ± 10.0	1.000
HADS-A (baseline)	8.5 ± 4.2	8.3 ± 3.6	0.898
HADS-D (baseline)	7.9 ± 6.3	6.9 ± 5.0	0.699

HADS, Hospital Anxiety and Depression Scale; HADS-A, anxiety subscale; HADS-D, depression subscale; NA, not applicable.

[a]Mann–Whitney *U* test, unless otherwise indicated.

Results

Clinical data

Four patients were lost during follow-up, and three patients (two classified as responders, one as a nonresponder) refused to undergo the second MRI scan. Complete clinical and imaging datasets could be obtained from 31 patients (17 responders, 14 nonresponders). Results from this group were similar to those in the present study and have been published in abstract form (Riederer et al., 2013). Eleven responders (9 females, 2 males) could be age and gender matched to 11 nonresponders (9 females, 2 males). Demographic and clinical data of this group are summarized in Table 1. Baseline characteristics did not differ significantly between responders and nonresponders. At follow-up, responders had significantly more reduction in number of headache days and significantly fewer days on pain medication than nonresponders. Most patients overused triptans and/or simple analgesics. All medications, including prophylactic medications, are listed in Table 2.

Follow-up 12 months after detoxification

Electronic charts were available from all patients. Twelve months after detoxification data were available for 10 responders and 8

Table 2. Medication in patients with medication-overuse headache

Patient No.	Responder	Sex	Age (years)	Prophylactic medications MRI 1	Prophylactic medications MRI 2	Acute headache medication	Contraceptives
1	Yes	M	43	Topiramate, duloxetine	Duloxetine	Triptans, SA	—
2	Yes	F	46	Pregabalin, trimipramine, venlafaxine	Pregabalin, trimipramine, venlafaxine	SA	—
3	Yes	F	26	—	Magnesium, riboflavin	SA	IUD (gestagen)
4	Yes	F	23	Magnesium, riboflavin, topiramate, β blockers	—	Triptans, SA	—
5	Yes	F	41	Valproate, magnesium	Riboflavin, candesartan	Triptans, SA	—
6	Yes	F	42	Lamotrigine	Topiramate	Triptans, CA	—
7	Yes	M	50	Venlafaxine	Venlafaxine, lamotrigine, trazodone	Triptans, SA	—
8	Yes	F	46	—	Venlafaxine	Triptans	Oral contraceptive
9	Yes	F	48	—	—	Triptans	—
10	Yes	F	51	Magnesium	Magnesium, metoprolol	SA	—
11	Yes	F	44	—	Valproate	Triptans	—
12	No	M	50	Valproate, mirtazapine, riboflavin	Trazodone, duloxetine	Triptans, SA	—
13	No	F	42	Magnesium	Metoprolol	Triptans, SA	Vaginal ring
14	No	F	23	—	Venlafaxine, riboflavin, magnesium	SA	Oral contraceptive
15	No	F	53	—	—	Triptans	.-
16	No	F	45	Riboflavin, magnesium	Venlafaxine, magnesium	Triptans	—
17	No	F	56	—	Topiramate	Triptans, SA	—
18	No	F	45	Topiramate	Topiramate	SA	—
19	No	F	54	Magnesium, riboflavin, pregabalin	—	Triptans	—
20	No	F	21	Magnesium	Topiramate	SA	—
21	No	M	44	Citalopram	Riboflavin	SA, triptans	—
22	No	F	54	Mirtazapin	Mirtazapin, venlafaxine, magnesium	SA	—

CA, Combination analgesics; IUD, intrauterine device; SA, simple analgesics; M, male; F, female.

nonresponders. Two responders had relapsed to MOH after 12 months. Nonresponders continued to have chronic headaches.

Imaging data

In responders, GM in the midbrain ($x = -5, y = -34, z = -8$; $T = 6.12$, $p = 0.006$, ROI corrected; cluster size, $k = 21$ voxels) decreased significantly after medication withdrawal (Fig. 1). In contrast, in nonresponders the GM between scans 1 and 2 was not significantly different. In all patients, GM in the significant midbrain cluster (Fig. 1) was extracted for scans 1 and 2. The difference in extracted GM between scans 1 and 2 correlated positively with treatment response (Spearman's $\rho = 0.500$, $p = 0.018$; corrected for age: $\rho = 0.551$, $p = 0.010$; i.e., greater GM reduction was associated with greater treatment response). The difference in extracted GM in the midbrain did not correlate with the reduction of days per month with acute medication intake (Spearman's $\rho = 0.161$, $p = 0.473$). No other regions showed significant GM decreases in responders and nonresponders.

Then, we defined T-contrasts to identify regions where GM would increase significantly from scan 1 to scan 2. No significant clusters were identified in responders or nonresponders.

Subsequently, we defined T-contrasts to identify GM increases or decreases between responders and nonresponders at baseline. Nonresponders had significantly less GM in the right OFC ($x = 8, y = 32, z = -26$; $T = 5.43$, $p = 0.012$, SVC corrected; cluster size, $k = 26$ voxels). Extracted GM in this cluster correlated positively with treatment response (Spearman's $\rho = 0.687$, $p < 0.001$; Fig. 2). This correlation persisted when corrected for age (Spearman's $\rho = 0.618$, $p = 0.003$).

No significant correlation between GM at baseline and days with pain medication per month were found.

Discussion

In this study, we investigated whether GM changes related to MOH such as increased GM in the midbrain and decreased GM in frontal regions are reversible after detoxification. The main finding was that GM in the midbrain, which had been found to be increased compared with healthy controls in a previous study (Riederer et al., 2012), significantly decreased only in patients who responded to treatment (i.e., those who had at least a 50% reduction in number of headache days). Nonresponders showed no significant changes between scans 1 and 2. The magnitude of GM reduction correlated positively with treatment response. In addition, we found that nonresponders had less GM in the OFC at baseline and a positive correlation of GM in this region with response to treatment (i.e., more GM at baseline was associated with a greater reduction of headache days at follow-up).

We suggest that a decrease of GM in the midbrain may indicate neuronal plasticity related to restitution of a facilitatory/inhibitory balance within the descending pain-modulating systems.

Brainstem dysfunction has been suggested in migraine (Pietrobon and Striessnig, 2003). It has been observed that electrical stimulation for pain other than headache (Raskin et al., 1987; Veloso et al., 1998) or lesions in the PAG (Haas et al., 1993; Goadsby, 2002) can cause migraine-like headaches in previously migraine-free subjects. Structural abnormalities include increased GM in migraine (Rocca et al., 2006) and progressive perturbation of iron homeostasis in episodic and chronic migraine (Welch et al., 2001). Functional neuroimaging studies reported increased metabolism in the brainstem during spontaneous migraine attacks (Weiller et al., 1995; Afridi et al., 2005). Areas of increased metabolism probably included the dorsal raphe nucleus (DRN) located ventrally to the PAG and the locus ceruleus (Weiller et al., 1995).

Based on *Duvernoy's Atlas of the Human Brain Stem and Cerebellum* (Naidich et al., 2009), the longitudinal GM decreases observed in our study included the PAG, adjacent midbrain reticular formation with nucleus cuneiformis (NCF), and the DRN.

The PAG has a major role in integrated behavioral responses of an individual to pain or external stimuli such as threat, coordinating specific patterns of cardiovascular, motor, and pain modulatory responses, according to the type of stress and the individual's perception to support active (e.g., fight or flight) or passive coping strategies (Benarroch, 2012). The PAG consists of

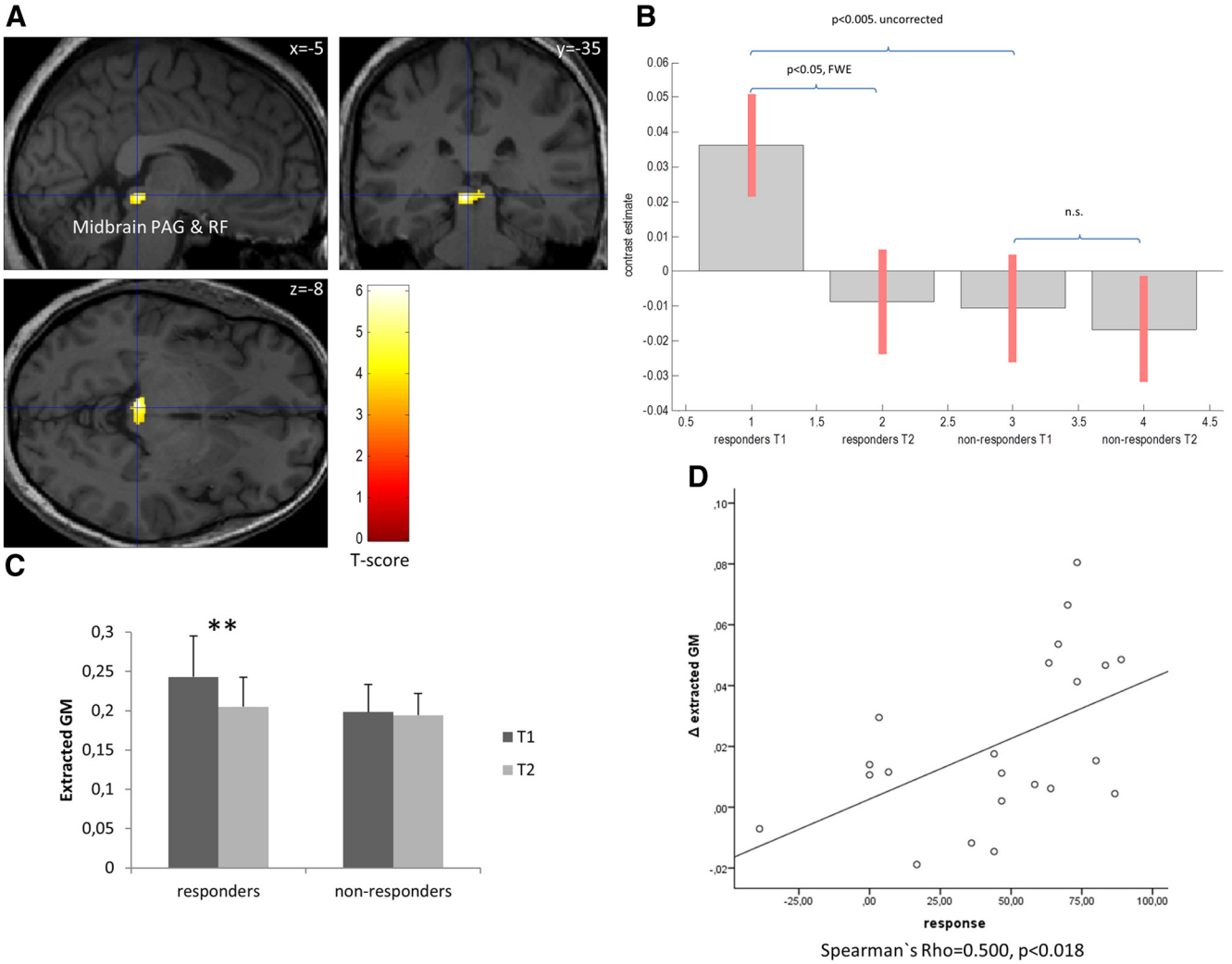

Figure 1. ***A***, Voxels with significant GM decrease in responders after detoxification projected on an MRI of a patient with MOH. Voxels include the PAG and midbrain reticular formation (RF). The right side in the coronal section and the lower side in the axial section correspond to the right patient side. For display, results were thresholded at $p < 0.001$, uncorrected. Slice locations are given in MNI space. ***B***, Plots of effect size (parameter β estimates in centered arbitrary units, 90% CI) from SPM analyses in the global maximum. The *x*-axis indicates time points of MRI scans for responders (T1, before detoxification; T2, after detoxification). Only responders show a significant GM decrease in the midbrain from scan 1 to scan 2 [repeated-measures ANOVA, $p < 0.05$, corrected for multiple comparisons with familywise error (FWE) across the ROI]. Exploratory analyses showed that responders had more GM in the midbrain at baseline compared with nonresponders (two-sample *t* test, $p < 0.005$, uncorrected). ***C***, GM volumes in the significant cluster from ***A*** extracted from individual scans. $^{**}p < 0.001$, paired *t* test. ***D***, The magnitude of gray matter volume reduction correlates with reduction in the number of headache days per month in percentage from baseline (Spearman's $\rho = 0.500$, $p < 0.018$).

distinct longitudinal columns that receive selective afferents from the forebrain including, OFC regions, brainstem, and sensory neurons from the dorsal horn and trigeminal nuclei (Behbehani, 1995; Benarroch, 2012). It is a substantial component of the descending pain-modulatory network and exerts an inhibitory or excitatory control on nociceptive transmission via the RVM, which in turn projects to the spinal and medullary dorsal horns (Heinricher et al., 2009).

The NCF is located in the midbrain reticular formation and has been related to the descending pain-modulating systems, acting in concert with the PAG (Dunckley et al., 2005). It is reciprocally connected with the PAG, receives input from forebrain regions including amygdala and hypothalamus, and projects to the RVM (Mantyh, 1983; Zemlan and Behbehani, 1988; Bernard et al., 1989; Hadjipavlou et al., 2006). The NCF is activated by nociceptive stimuli and has been implicated in central sensitization in fMRI studies (Dunckley et al., 2005; Zambreanu et al., 2005). The NCF was found hypofunctional in individuals experiencing migraines (Moulton et al., 2008). The NCF, like the PAG and RVM, contains functionally distinct classes of neurons that can enhance nociception ("ON cells") or inhibit nociception ("OFF cells") (Fields et al., 1983; Heinricher et al., 1987; Haws et al., 1989).

Decreased descending inhibition or increased facilitation to the medullary dorsal horn, with increased sensitization and consequently increased nociception from dural and meningeal vascular afferents, has been suggested to be involved in the development of chronic daily headache (Okada-Ogawa et al., 2009). Consistently, patients with active MOH have increased pain perception and nociceptive withdrawal reflex in cephalic and extracephalic regions, which normalize after detoxification (Perrotta et al., 2010, 2012; Munksgaard et al., 2012). Possible mechanisms probably include sensitization in trigeminal ganglia and medullary dorsal horn induced by triptans or opiates (Okada-Ogawa et al., 2009; De Felice et al., 2010).

In our data, GM changes also included the DRN, a major source of widespread serotonergic projections to the forebrain (Michelsen et al., 2007). Alterations in serotonergic transmission

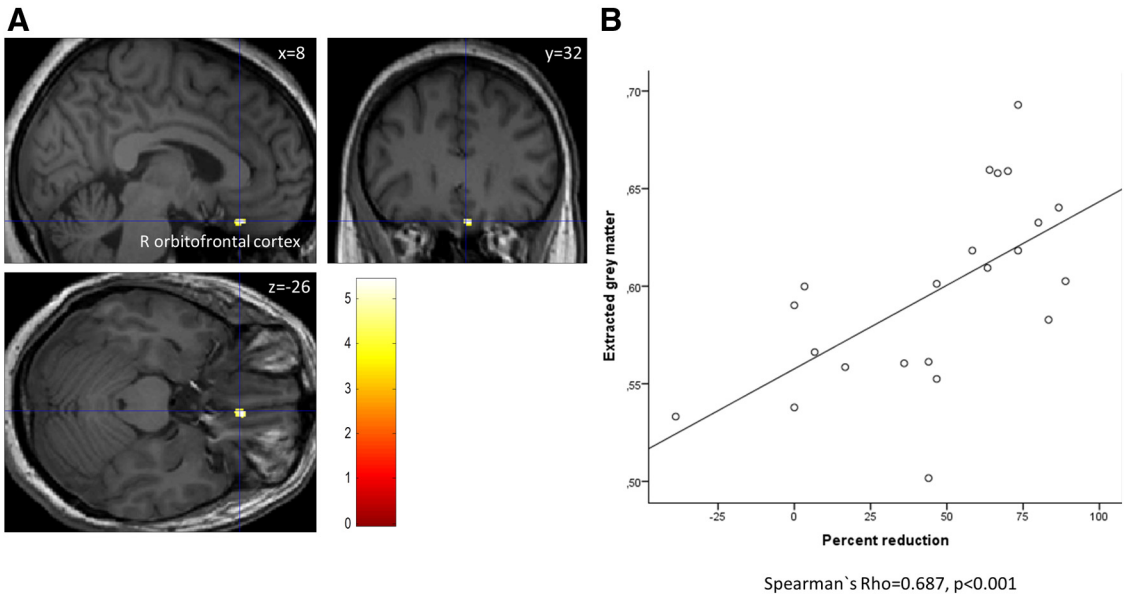

Figure 2. ***A***, Responders have significantly more gray matter volume than nonresponders at baseline in the orbitofrontal cortex. R indicates right. ***B***, Extracted gray matter in this region correlates positively with relative reduction in number of headache days per month (Spearman's $\rho = 0.687$, $p < 0.001$; i.e., more gray matter volume at baseline was associated with a greater reduction of headache days at follow-up). The *x*-axis indicates the reduction of number of days with headache per month in percentage from baseline. The *y*-axis indicates gray matter volume in arbitrary units.

have been reported in models of MOH, including an upregulation of 5-HT_{2A} receptors in cortical projection areas (Supornsilpchai et al., 2010; Bongsebandhu-phubhakdi and Srikiatkhachorn, 2012). Triptans are selective 5-$HT_{1B/D}$ receptor agonists, binding also in the PAG, where they influence nociception, possibly via serotonergic mechanisms (Bartsch et al., 2004; Lambert, 2005). Chronic triptan administration decreased 5-$HT_{1B/D}$ receptor mRNA in the trigeminal ganglion and the basilar artery (Reuter et al., 2004), and increased the rate of 5-HT synthesis in projection areas, probably related to the downregulation of inhibitory 5-HT_1 autoreceptors (Dobson et al., 2004). Similarly, a downregulation of 5-$HT_{1B/D}$ receptors and an increased 5-HT synthesis could be assumed in the midbrain. In our data, no significant correlation between GM decrease and reduction of medication intake, or GM at baseline and medication intake was found.

Due to methodological limitations, a precise mechanism cannot be delineated since the histopathological correlates of GM changes are not yet fully understood. Whereas it seems evident that neuronal loss and gliosis is associated with GM decreases (Riederer et al., 2008), the reverse cannot be concluded, since reversible GM decreases have been observed in pain syndromes (Rodriguez-Raecke et al., 2009). Stimulus-dependent GM increases have been demonstrated in learning tasks (Draganski et al., 2004) and repetitive painful stimuli (Teutsch et al., 2008). GM changes have been related to neuronal or glial cell genesis or degeneration; increases/decreases in cell size, spine, or synapse turnover; or changes in blood flow or interstitial fluids (May, 2011), and may reflect a combination of these.

In our data, nonresponders had less GM in the right OFC at baseline, and a positive correlation between GM and treatment response was found. Formally, these patients are to be diagnosed as chronic migraine according to Headache Classification Subcommittee of the International Headache Society (2004) criteria. Metabolic and functional changes within the OFC have been previously suggested in MOH. In a PET study, all regions that have been shown to be dysmetabolic in active MOH returned to normal after detoxification, except for the OFC, where hypometabolism persisted (Fumal et al., 2006). Neuropsychological studies have shown that poor performance in tasks related to OFC function in MOH patients predicts poor outcome after withdrawal (Gómez-Beldarrain et al., 2011). Dysfunction of OFC, particularly on the right side, has been implicated in maladaptive decision making, and dysfunction of OFC has been related to drug addiction (Tranel et al., 2002; Tanabe et al., 2009; Lucantonio et al., 2012). Patients with MOH fulfill certain criteria of substance dependence, with its severity being predictive for the outcome after detoxification (Fuh et al., 2005; Radat et al., 2008; Lundqvist et al., 2012). OFC dysfunction might thus interfere with internal control to repeated medication intake; in addition, OFC projections to the PAG may influence its pain modulation.

While there are several cross-sectional morphometric studies on headache (May, 2009), there are only few VBM studies investigating potentially reversible pain syndromes longitudinally. Obermann et al. (2009) found a GM decrease in the dorsolateral prefrontal cortex and in the anterior cingulate cortex in patients who developed chronic post-traumatic headache. In the follow-up investigation, after 12 months, when patients had become pain free, GM decreases were found to be reversible. In addition, an increase in GM was found after 12 months in the thalamus and in the midbrain, suggesting an association with antinociceptive mechanisms.

Two other studies investigated GM changes associated with osteoarthritis of the hip before and after surgery (Rodriguez-Raecke et al., 2009; Gwilym et al., 2010). Both studies reported reversible GM changes. The first study (Rodriguez-Raecke et al., 2009) reported GM increases in the dorsolateral prefrontal cortex, anterior cingulate cortex, and brainstem, whereas the other study (Gwilym et al., 2010) found reversible GM atrophy in the thalami. All aforementioned VBM studies reported GM increases within a time period of 4–12 months.

In our study, we did not find any GM increases in frontal, especially OFC, regions, possibly because patient samples and observation periods differed, which was against our expectations. Also, changes in GM within structures of the reward system, such as the ventral striatum, and changes in the thalamus did not reverse after detoxification.

A limitation of this study might be that possible influences of prophylactic medication or a combination of medications cannot be ruled out entirely. However, most patients were on prophylactic medication before and after detoxification. Antidepressants and anticonvulsants seem generally not to be associated with volumetric differences, according to a recent review (Hafeman et al., 2012).

Conclusions

Our data show that response to the withdrawal of acute headache medication is associated with the decrease of previously increased GM in the midbrain. The lack of longitudinal GM changes in other regions (e.g., the ventral striatum and OFC) might underpin the idea that these patients are prone to relapse and deserve dedicated care, including multimodal treatment strategies. Future studies should investigate correlations of GM changes with behavioral measures assessing dependence and impulse control. Animal models of medication-induced sensitization should focus on midbrain structures such as the PAG and NCF.

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